

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

WO 98/35666

PCT/US98/03388

FORMULATIONS OF NANOPARTICLE NAPROXEN TABLETS

5

BACKGROUND OF THE INVENTION10 **Field of the Invention**

The present invention relates to formulations of nanoparticulate naproxen in the form of compressed tablets having increased rate of dissolution in vitro, increased rate of naproxen absorption in vivo, decreased fed/fasted variability and decreased variability in absorption.

15

Reported Developments

Naproxen as an anti-inflammatory, analgesic and antipyretic drug is well-known and has been widely used in the pharmaceutical industry. Its delivery characteristics were studied and addressed in publications and patents. Its pharmaceutical forms of delivery include tablets, capsules and liquids. Delivery characteristics and forms are disclosed, for example in U.S. Patent Nos. 4,780,320; 4,888,178; 4,919,939; 4,940,588; 4,952,402; 5,200,193; 5,354,556; 5,462,747; and 5,480,650.

20

WO 98/35666

PCT/US98/03388

SUMMARY OF THE INVENTION

We have discovered that pharmaceutical compositions containing surface modified nanoparticulate naproxen compressed into tablets exhibit increased rate of dissolution in vitro and in vivo when compared to conventional microparticulate formulations of naproxen. In addition they provide for fast absorption, decreased variability in absorption and decreases the fed/fasted variability in absorption.

More particularly, in accordance with this invention, there are provided naproxen particles having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an average particle size of less than about 400 nm compressed or compacted into tablets using a pharmaceutically acceptable carrier.

In another aspect of the invention, there is provided a method of preparing the above-described particles and tablets containing said particles comprising the steps of:

- a) dispersing powdery naproxen in a liquid dispersion medium and wet grinding the naproxen in the presence of rigid grinding media to obtain nanoparticles of naproxen; and
- b) compressing the so-obtained nanoparticles into tablets using a pharmaceutically acceptable carrier.

In another aspect of the invention, there is provided a method of preparing the above-described particles and tablets containing said particles comprising the steps of:

- a) dispersing powdery naproxen in a liquid dispersion medium and wet grinding the naproxen in the presence of rigid grinding media to obtain nanoparticles of naproxen; and
- b) compacting the so-obtained nanoparticles into tablets using a pharmaceutically acceptable carrier.

In another aspect of the present invention, there is provided a method of treating a mammal requiring anti-inflammatory, analgesic or antipyretic treatment comprising: administering to the mammal the above-described pharmaceutical composition.

WO 98/35666

PCT/US98/03388

Advantageous features of this invention include, in addition to increased rate of dissolution, that the tablets exhibit: a hardness of greater than about 6 kp, preferably greater than about 10 kp; a friability of less than about 0.25%; and uniformity of content.

- 5 The pharmaceutical composition of the present invention in a compressed tablet form comprises based on % w/w:

Naproxen/Surface Modifier	42-58
Binding Agent	30-40
Filling Agent	10-15
Lubricating Agent	0.2-0.3
Other excipients	0-4

- 10 The pharmaceutical composition of the present invention in a compacted tablet form comprises based on % w/w:

Naproxen/Surface Modifier	65-80
Disintegrating Agent	10-20
Filling Agent	5-20
Lubricating Agent	0.4-0.6
Other excipients	0-4

- 15 In preparing the pharmaceutical composition of the present invention tableting ingredients which are well known in the art may be used.

Preferred ingredients used in the tablets of the present invention include:

- 20 Filling agents such as lactose monohydrate, lactose hydrous and various starches;
- Binding agents such as various celluloses, preferably low-substituted hydroxypropyl cellulose, and cross-linked polyvinylpyrrolidone;
- Disintegrating agents such as croscarmellose sodium;
- 25 Lubricating agents such as talc, magnesium stearate, stearic acid and silica gel; and
- Surface modifiers such as hydroxypropyl cellulose and polyvinylpyrrolidone.

WO 98/35666

PCT/US98/03388

The pharmaceutical tablets of the present invention have a time to peak plasma concentration of less than about 2 hours, preferably 1 hour, and preferably bioavailability greater than 23 mg h/l in one hour.

5

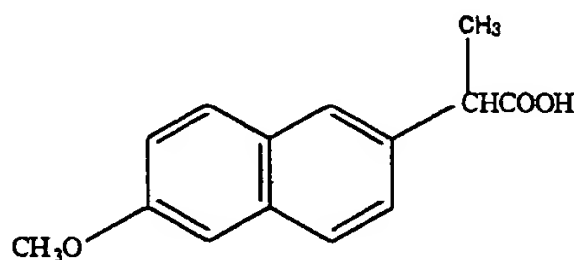
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides nanoparticulate naproxen formulations in combination with pharmaceutically acceptable excipients compressed into tablets.

10

Naproxen

Naproxen ((S)-6-methoxy- α -methyl-2-naphthaleneacetic acid) having the structural formula



15

is well known in the pharmaceutical industry under various trademarks, including NAPROSYN® and ANAPROX® and is used as an anti-inflammatory, analgesic and antipyretic drug. Its synthesis is described in U.S. Patent Nos. 3,904,682 and 4,009,197 which are incorporated herein by reference.

20

In human therapy it is of the utmost importance to provide dosage forms of naproxen which in the body of a patient delivers the required therapeutic amount of the drug and renders the drug bioavailable in a rapid and constant manner.

25

In the practice of the present invention, naproxen obtained from the supplier in powder form is made into nanoparticulate form by grinding techniques in the presence of a surface modifier.

Surface Modifiers

30

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight

WO 98/35666

PCT/US98/03388

oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and ionic surfactants.

Representative examples of surface modifiers include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available TweensTM, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these surface modifiers are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, poloxamers such as PluronicsTM F68 and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyoxamines such as TetronicsTM 908 (also known as PoloxamineTM908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, available from BASF, dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol OTTM, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, DuponolsTM P, which is a sodium lauryl sulfate, available from DuPont, TritonsTM X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, TweenTM 20 and TweenTM 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Specialty Chemicals; CarbowaxTM 3550 and 934, which are polyethylene glycols available from Union Carbide; CrodestaTM F-110, which is a mixture of sucrose stearate and sucrose distearate, available from Croda Inc., CrodestaTM SL-40, which is available from Croda, Inc., and SA9OHCO, which is C₁₈H₃₇CH₂(CON(CH₃)CH₂(CHOH)₄(CH₂OH)₂). Surface modifiers which have been found to be particularly useful include TetronicTM 908, the TweensTM, PluronicTM F-68 and polyvinylpyrrolidone. Other useful surface modifiers include:

decanoyl-N-methylglucamide;
n-decyl (β-D-glucopyranoside);
n-decyl (β-D-maltopyranoside);

WO 98/35666

PCT/US98/03388

5 n-dodecyl (β -D-glucopyranoside);
n-dodecyl (β -D-maltoside);
heptanoyl-N-methylglucamide;
n-heptyl-(β -D-glucopyranoside);
n-heptyl (β -D-thioglucoside);
n-hexyl (β -D-glucopyranoside);
nonanoyl-N-methylglucamide;
n-nonyl (β -D-glucopyranoside);
10 octanoyl-N-methylglucamide;
n-octyl-(β -D-glucopyranoside);
octyl (β -D-thioglucopyranoside); and the like.

15 Another useful surface modifier is tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type; also known as superinone or triton). This surface modifier is commercially available and/or can be prepared by techniques known in the art.

20 Another preferred surface modifier is p-isononylphenoxypoly(glycidol) also known as Olin-10GTM or Surfactant 10-G, is commercially available as 10GTM from Olin Chemicals, Stamford, Connecticut.

25 Preferred surface modifiers can be selected from known non-ionic surfactants, including the poloxamines such as TetronicTM 908 (also known as PoloxamineTM 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, available from BASF, or TetronicTM 1508 (T-1508), or a polymer of the alkyl aryl polyether alcohol type, such as tyloxapol.

The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two-or more surface modifiers can be used in combination.

30 Tyloxapol (4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde) is a preferred surface modifier and is a nonionic liquid polymer of the alkyl aryl polyether alcohol type. Tyloxapol, also known as "Superinone", is disclosed as useful as a nonionic surface active agent in a lung surfactant composition in U.S. Patent No. 4,826,821 and as a stabilizing agent for 2-dimethylaminoethyl 4-n-butylaminobenzoate in U.S. Patent No.
35 3,272,700.

Most preferred for use in the direct compression tableting is polyvinylpyrrolidone. Most preferred for use in roller compaction tableting is hydroxypropyl cellulose.

WO 98/35666

PCT/US98/03388

Auxiliary Surface Modifiers

Particularly preferred auxiliary surface modifiers are those which impart resistance to particle aggregation during sterilization and include dioctylsulfosuccinate (DOSS), polyethylene glycol, glycerol, sodium dodecyl sulfate, dodecyl trimethyl ammonium bromide and a charged phospholipid such as dimyristoyl phosphatidyl glycerol. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

One preferred surface modifier is a block copolymer linked to at least one anionic group. The polymers contain at least one, and preferably two, three, four or more anionic groups per molecule.

Preferred anionic groups include sulfate, sulfonate, phosphonate, phosphate and carboxylate groups. The anionic groups are covalently attached to the nonionic block copolymer. The nonionic sulfated polymeric surfactant has a molecular weight of 1,000-50,000, preferably 2,000-40,000 and more preferably 3,000-30,000. In preferred embodiments, the polymer comprises at least about 50%, and more preferably, at least about 60% by weight of hydrophilic units, e.g., alkylene oxide units. The reason for this is that the presence of a major weight proportion of hydrophilic units confers aqueous solubility to the polymer.

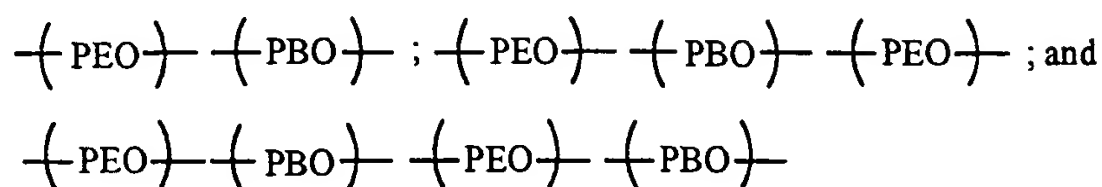
A preferred class of block copolymers useful as surface modifiers herein includes sulfated block copolymers of ethylene oxide and propylene oxide. These block copolymers in an unsulfated form are commercially available as Pluronics™. Specific examples of the unsulfated block copolymers include F68, F108 and F127.

Another preferred class of block copolymers useful herein include tetrafunctional block copolymers derived from sequential addition of ethylene oxide and propylene oxide to ethylene diamine. These polymers, in an unsulfated form, are commercially available as Tetronics™.

Another preferred class of surface modifiers contain at least one polyethylene oxide (PEO) block as the hydrophilic portion of the molecule and at least one polybutylene oxide (PBO) block as the hydrophobic portion. Particularly preferred surface modifiers of this class are diblock, triblock, and higher block copolymers of ethylene oxide and butylene oxide, such as are represented, for example, by the following structural formula:

WO 98/35666

PCT/US98/03388

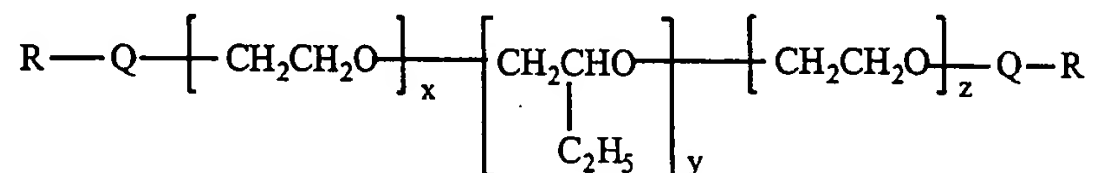


The block copolymers useful herein are known compounds and/or can be readily prepared by techniques well known in the art.

5

Highly preferred surface modifiers include triblock copolymers of the $-(\text{PEO})-(\text{PBO})-(\text{PEO})-$ having molecular weights of 3800 and 5000 which are commercially available from Dow Chemical, Midland, Michigan, and are referred to as B20-3800 and B20-5000. These surface modifiers contain about 80% by weight PEO. In a preferred embodiment, the surface modifier is a triblock polymer having the structure:

10



Q is an anionic group

15

wherein R is H or a metal cation such as Na⁺, K⁺ and the like,
 x is 15-700,
 Y is 5-200 and
 z is 15-700.

20

Reducing the Particle Size of Naproxen to Nanoparticles

25

The nanoparticles of naproxen can be prepared in a method comprising the steps of dispersing the naproxen powder in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of naproxen to an effective average particle size of less than about 400 nm. The particles are reduced in size in the presence of a surface modifier

30

The naproxen powder can be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the naproxen in the liquid medium can vary from about 0.1 - 60%, and preferably is from 5 - 40% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can

WO 98/35666

PCT/US98/03388

vary from about 0.1 to about 90%, and preferably is 1-75%, more preferably 20-60%, by weight based on the total combined weight of the naproxen and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise.

5 The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 400 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the naproxen and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no
10 large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

 The mechanical means applied to reduce the particle size of naproxen conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a
15 vibratory mill, and media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal
20 balance between efficient particle fragmentation and media erosion.

 The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times
25 of one minute up to several hours) have provided the desired results using a high shear media mill.

 The particles of naproxen must be reduced in size at a temperature which does not significantly degrade naproxen. Processing temperatures of less than about 30 - 40°C are
30 ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Control of the temperature, e.g., by jacketing or immersion of the milling chamber in ice water
35 are contemplated. Processing pressures from about 1 psi (0.07 kg/cm²) up to about 50 psi (3.5

WO 98/35666

PCT/US98/03388

kg/cm²) are contemplated. Processing pressures range from about 10 psi (0.7 kg/cm²) to about 20 psi (1.4 kg/cm²).

After attrition is completed, the grinding media is separated from the milled particulate product using conventional separation techniques, such as by filtration, sieving through a mesh screen, and the like.

Grinding Media

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. We have found that zirconium oxide, such as 95% ZrO₂ stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. However, other media, such as stainless steel, titania, alumina, and 95% ZrO₂ stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 3 g/cm³.

Polymeric Grinding Media

The grinding media can comprise particles, preferably substantially spherical in shape, e.g., beads, consisting essentially of polymeric resin. Alternatively, the grinding media can comprise particles comprising a core having a coating of the polymeric resin adhered thereon.

In general, polymeric resins suitable for use herein are chemically and physically inert, substantially free of metals, solvent and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric resins include crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene, styrene copolymers, polycarbonates, polyacetals, such as Delrin™, vinyl chloride polymers and copolymers, polyurethanes, polyamides, poly(tetrafluoroethylenes), e.g., Teflon™, and other fluoropolymers, high density polyethylenes, polypropylenes, cellulose ethers and esters such as cellulose acetate, polyhydroxymethacrylate, polyhydroxyethyl acrylate, silicone containing polymers such as polysiloxanes and the like. The polymer can be biodegradable. Exemplary biodegradable polymers include poly(lactides), poly(glycolide) copolymers of lactides and glycolide, polyanhydrides, poly(hydroxyethyl methacrylate), poly(imino carbonates), poly(N-

WO 98/35666

PCT/US98/03388

acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes). In the case of biodegradable polymers, contamination from the media itself advantageously can metabolize in vivo into biologically acceptable products which can be eliminated from the body.

5

The polymeric resin can have a density from 0.8 to 3.0 g/cm³. Higher density resins are preferred inasmuch as it is believed that these provide more efficient particle size reduction.

The media can range in size from about 0.1 to 3 mm. For fine grinding, the particles preferably are from 0.2 to 2 mm, more preferably, 0.25 to 1 mm in size.

10

In a preferred grinding process the particles are made continuously. The continuous method comprises the steps of continuously introducing naproxen into a milling chamber, contacting the naproxen with grinding media while in the chamber to reduce the particle size of naproxen, continuously removing the naproxen from the milling chamber.

15

The grinding media is separated from the milled particulate naproxen using conventional separation techniques, in a secondary process such as by simple filtration, sieving through a mesh filter or screen, and the like. Other separation techniques such as centrifugation may also be employed.

20

Particle Size

As used herein, particle size is determined on the basis of number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. When photon correlation spectroscopy (PCS) is used as the method of particle sizing the average particle diameter is the Z-average particle diameter known to those skilled in the art. By "an effective average particle size of less than about 400 nm" it is meant that at least 90% of the particles, by weight, have a particle size of less than about 400 nm when measured by the above-noted techniques. In preferred embodiments, the effective average particle size is less than about 300 nm and more preferably less than about 250 nm. In some embodiments, an effective average particle size of less than about 100 nm has been achieved. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average particle size, e.g., 400

35

WO 98/35666

PCT/US98/03388

nm. In particularly preferred embodiments essentially all of the particles have a size less than 400 nm. In some embodiments, essentially all of the particles have a size less than 250 nm.

5 The relative amount of naproxen and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the hydrophilic lipophilic balance (HLB) of the stabilizer, the melting point of the stabilizer, its water solubility, the surface tension of water solutions of the stabilizer, etc. The surface modifier preferably is present in an amount of about 0.1-10 mg per square meter surface area of
10 the naproxen. The surface modifier can be present in an amount of 0.1-90%, preferably 20-60% by weight based on the total weight of the dry particle.

The resulting dispersion constituting a part of this invention is stable and consists of the liquid dispersion medium and the above-described naproxen.

15

Pharmaceutical compositions according to this invention include the particles of naproxen and surface modifier and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. A method of treating a mammal in accordance with this invention comprises the step of administering to the
20 mammal in need of treatment an effective amount of the composition. It is a particularly advantageous feature that the pharmaceutical compositions of this invention exhibit unexpectedly rapid absorption. Furthermore, it is contemplated that the naproxen particles of this invention provide more rapid onset of drug action in oral applications.

25 While applicants do not wish to be bound by theoretical mechanisms, it is believed that the surface modifier hinders the flocculation and/or agglomeration of the particles by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation. Alternatively, if the surface modifier has ionic groups, stabilization by electrostatic repulsion may result.

30

The Process of Preparing The Tablets

A process of preparing the naproxen tablets of the present invention include the steps of:

35

- (a) using the below-described method to obtain spray-dried nanoparticles of naproxen;

WO 98/35666

PCT/US98/03388

- (b) screening by sieve the spray dried nanoparticles to obtain uniform particles of less than about 20 mesh;
- (c) blending the nanoparticulate naproxen with tableting excipients;
- (d) compressing the uniform particles into tablets using a tableting apparatus; and
- (e) film coating the tablets.

10 Spray Drying of Naproxen Nanosuspensions

The spray drying process is used to obtain an "intermediate" nanoparticulate powder subsequent to the milling process by which naproxen is transformed into nanoparticles. In the spray drying process the high-solids naproxen nanosuspension and a stabilizer, such as polyvinylpyrrolidone, is fed to an atomizer using a peristaltic pump and atomized into a fine spray of droplets. The spray is contacted with hot air in the drying chamber resulting in the evaporation of moisture from the droplets. The so-produced spray is passed into a cyclone where the powder is separated and collected.

20 At the completion of the spray drying process, the collected spray dried intermediate contains naproxen nanoparticles suspended in a solid polymer matrix of the stabilizer, i.e., polyvinylpyrrolidone. The moisture content of the intermediate is controlled by the operating conditions of the spray drying process. The characteristics of the nanoparticulate powder are critical to the development of a free flowing powder that can be blended with other excipients suitable for a directly compressible tablet formulation.

Example 1 illustrates the direct compression tablet process while Example 2 illustrates the roller compaction process.

WO 98/35666

PCT/US98/03388

Example 1 (Direct Compression Process)
DC/Naproxen NP

5 **Media Milling of Naproxen/Povidone K-29/32 Nanosuspensions**

A high-energy media milling process was used to manufacture a 30 kg batch of 40% (w/w) naproxen, USP 3% (w/w) povidone K-29/32, USP nanosuspension.

10 A stabilizer solution containing 0.90 kg povidone K-29/32 (polyvinylpyrrolidone), USP, was dissolved into 15.2 kg purified water, USP, in a 10 gallon tank using a propeller mixer. Naproxen, USP (12.0 kg) was dispensed incrementally into the stabilizer solution in the tank until the entire amount had been added to the tank and the contents of the tank appeared well mixed. A mixer/emulsifier was used to wet the solids. The operation was complete when no visual evidence of unwetted solids was observed.

15

A media mill was charged with 0.5 mm SDy-20 Polymeric Media (supplied by Eastman Kodak, Rochester, NY) at a 80% load. The media mill and tank were connected in a closed-loop configuration with a peristaltic pump installed at the inlet of the media mill grinding chamber to circulate the product nanosuspension at 1.0 kg/min. The agitator speed of the media mill was 20 1900 RPM. The media milling operation was complete when a mean volume particle size distribution of 90% <400 nm was obtained.

Spray Drying of Naproxen/Povidone K-29/32 Nanosuspensions

25 Following the media milling operation, the product 40% (w/w) naproxen, USP, 3% (w/w) povidone, K-29/32 (polyvinylpyrrolidone), USP nanosuspension was spray dried to manufacture 12.9 kg (theoretical yield) of powder, or "spray dried intermediate". Operating conditions were selected to maintain an inlet temperature of 150°C and an outlet temperature of 65°C. Acceptable product spray-dried intermediate have a moisture content not to exceed 1.0% (w/w).

30

WO 98/35666

PCT/US98/03388

Direct Compression Tablet Manufacturing

Using the spray dried intermediate, tablets containing 200 mg naproxen and having a total average weight of 416 mg were manufactured using a direct compression process. The spray dried intermediate (9.56 kg) and low substituted hydroxypropyl cellulose (L-HPC) (Grade
5 LH-11)(2.22 kg) were sieved through a 20 mesh screen. The screened material was added to a 10 cu. ft. blender and blended for 5 minutes. Again, using a 20 mesh screen, fast flow lactose (6.67 kg) was sieved, added to the blender and blended for 7.5 minutes. Magnesium stearate, NF (44.47 g) was hand screened through a 40 mesh screen, added to the blender and blended for an additional 2.5 minutes. At the completion of blending, the contents of the blender were
10 discharged into a tared collection container.

Compression of tablet cores was completed on a tablet press. The blended material was loaded into the feed hopper and force-fed into the die cavities using an automatic feeder. The tablet press operating conditions are set to meet thickness (5.25 mm), hardness (10 kp), and
15 weight (416 mg) specifications.

Coating of Core Tablets

Upon completion of the compression operation, a Vector-Freund Hi-Coater, Model HC-24 (4 Baffles) was used to apply a film-coating on the tablet cores from a 15%(w/w) Opadry
20 Light Orange coating suspension. The coating pan was charged with 15 kg of compressed cores. The pan speed was adjusted to 14 RPM and the tablet bed was preheated to 45°-50°C prior to beginning the spray coating operation. Coating was continued until a nominal 3% weight gain was achieved.

WO 98/35666

PCT/US98/03388

Example 2 (Roller Compaction Process)
RC/Naproxen NP

Media Milling of Naproxen/HPC Nanosuspensions

5 A high-energy media milling process was used to manufacture a 10 kg batch of 25% (w/w) naproxen, USP, 2.5% (w/w) hydroxypropyl cellulose (HPC), USP nanosuspension.

10 A stabilizer solution was prepared by dissolving 0.23 kg HPC, USP, in 6.53 kg purified water, USP, in a 20L container using a propeller mixer. Naproxen, USP (2.25 kg) was dispensed incrementally into the stabilizer solution until the entire amount had been added. The operation was complete when no visual evidence of unwetted solids was observed and the contents of the container appeared well-mixed.

15 A media mill was charged with 0.5 mm SDy-20 Polymeric Media (supplied by Eastman Kodak, Rochester, NY) at a 80% load. The media mill and container were connected in a closed-loop configuration with a peristaltic pump installed at the inlet of the media mill grinding chamber to circulate the product nanosuspension at 100 ml/min. The agitator speed of the media mill was operated at a speed of 2250 RPM. The media milling operation was complete when the mean volume particle size distribution of 90% <400 nm was obtained.

20

Spray Drying of Naproxen/HPC Nanosuspensions

25 Following the media milling operation, the product 25% (w/w) naproxen, USP, 2.5% (w/w) HPC, USP nanosuspension was spray dried to manufacture 2.5 kg (theoretical yield) of spray dried intermediate. The spray drier was assembled in a co-current configuration using a rotary atomization nozzle. The nanosuspension was fed to the rotary atomizer operated at 150 RPM using a peristaltic pump. The operating conditions of the spray dryer require a heater power setting of 5 kW to maintain an inlet temperature of 150°C and an outlet temperature of 65°C at a product feed rate of approximately 65 g/min. Acceptable product spray-dried intermediate will have a moisture content not to exceed 1.0% (w/w).

30

WO 98/35666

PCT/US98/03388

Dry Granulation

A dry granulation operation was used to manufacture tablets containing 200 mg naproxen and having a total average weight of 400 mg. Required amounts of naproxen/HPC spray dried intermediate (0.88 kg) and croscarmellos sodium (0.18 kg) are hand screened through a 60 mesh
5 screen and blended in a 16 qt. twin shell blender for 15 minutes. The blended material was compacted using a roller compactor at 12 tons pressure and feed auger speed of 20 RPM. The compacted material was granulated using a CoMil at 925 RPM with 0.75R screen.

Blending

10 At the completion of the granulation, lactose hydrous, USP (0.15 kg) was screened through a 80 mesh screen and blended with the above granulation for up to 15 minutes in a 16 qt. twin shell blender. Magnesium stearate, USP (6g) was screened through a 80 mesh screen, added to the 16 qt. twin shell blender and blended for up to 5 minutes.

15 Compression

The blended materials were discharged and compressed into tablets using a tablet press with caplet shaped tooling. The blended materials were loaded into the feed hopper and gravity-fed into the die cavities. The tablet press operating conditions were set to meet thickness (5.25 mm), hardness (10 kp), and weight (400 mg) specifications.

20

The process of manufacturing the tablets by direct compression is shown in Process Flow Diagram A while the process of manufacturing the tablets by roller compaction is shown in Process Flow Diagram B.

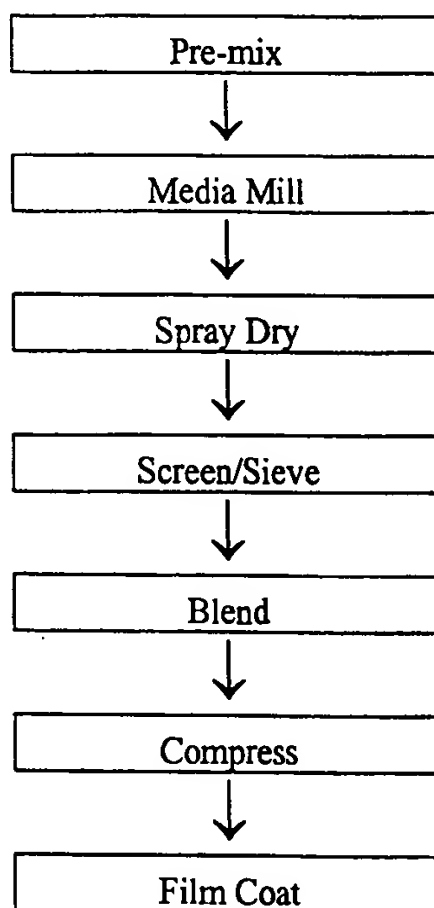
WO 98/35666

PCT/US98/03388

PROCESS FLOW DIAGRAM - A**Direct Compression**

5

10



WO 98/35666

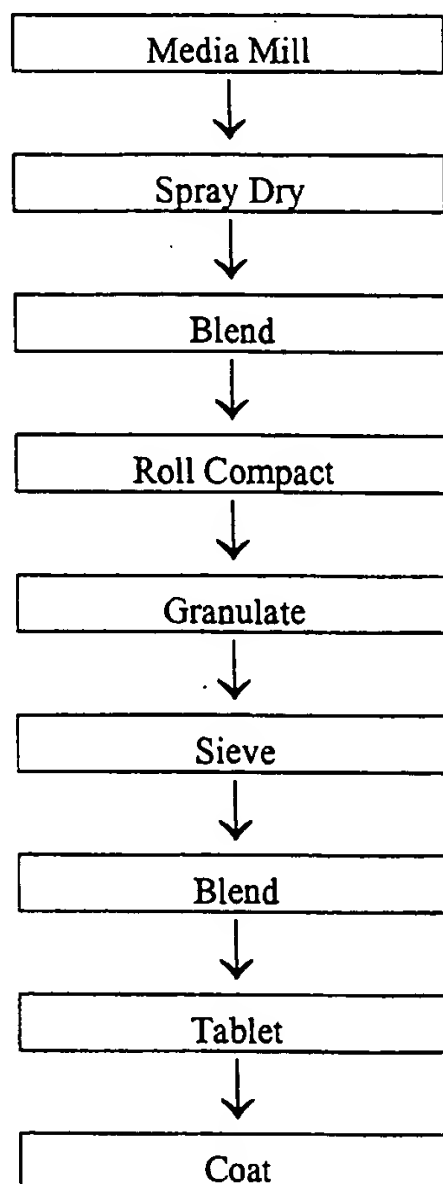
PCT/US98/03388

PROCESS FLOW DIAGRAM - B
Roller Compaction

5

10

15



Following the above-described process representative tablets containing the ingredients shown in the Examples are prepared.

WO 98/35666

PCT/US98/03388

Non-film coated tablets of the formulation of Example 1 made by an analogous process were tested for hardness; the results are shown hereunder.

HARDNESS (kp)

5

Time (weeks)	5°C	25°C	40°C
0	11.6±1.5	11.6±1.5	11.6±1.5
2	11.1±1.4	11.4±1.0	12.2±1.3
4	10.7±1.1	11.4±1.0	12.5±1.4
6	10.8±1.5	11.2±1.5	11.5±1.7
12	10.7±2.6	12.1±1.4	12.8±1.4
24	11.4±1.8	11.0±2.2	11.6±1.2

Non-film coated tablets of the formulation of Example 1 made by an analogous process were tested for disintegration vs time; results are shown hereunder.

10

DISINTEGRATION (kp)

Time (weeks)	5°C	25°C	40°C
0	---	---	---
2	2:04±0:16	2:04±0:17	2:05±0:07
4	2:18±0:17	2:16±0:31	2:03±0:07
6	2:15±0:16	2:09±0:05	2:01±0:12
12	2:25±0:16	2:19±0:10	2:18±0:17
24	2:26±0:09	2:02±0:14	2:30±0:08

Using the process of Example 1, tablets from the formulation of Examples 3, 4 and 5 were prepared.

15

WO 98/35666

PCT/US98/03388

Example 3

Ingredients	mg/Tablet	% of Tablet
Naproxen	200	47.7
HPC-SL	18	4.3
L-HPC (grade LH-11)	50	11.9
FastFlo Lactose	150	36.1
Magnesium Stearate	1	0.25
Total	419	100.05

Example 4

5

Ingredients	mg/Tablet	% of Tablet
Naproxen	200	48.1
PVP	15	3.6
PVPP	50	12.0
FastFlo Lactose	150	35.1
Magnesium Stearate	1	0.25
Total	416	99.05

Example 5

Ingredients	mg/Tablet	% of Tablet
Naproxen	200	47.7
HPC-SL	18	4.3
PVPP	50	11.9
FastFlo Lactose	150	35.8
Magnesium Stearate	1	0.25
Total	419	99.95

Surface stabilizers for nano-naproxen:

10

PVP = Polyvinylpyrrolidone

HPC-SL = Hydroxypropyl Cellulose (super low viscosity)

Binders:

L-HPC = Low-substitution HPC, insoluble (binder)

PVPP = Crospovidone, insoluble, cross-linked PVP (binder)

WO 98/35666

PCT/US98/03388

Tablets of Examples 3-5 were tested for hardness; the results are shown hereunder.

HARDNESS (kp)

REFRIGERATION	Example 3	Example 4	Example 5
Initial	9.5±0.7	9.0±2.0	6.9±0.4
2 weeks	8.7±1.1	7.1±1.1	6.5±0.7
4 weeks	9.2±1.2	8.4±1.7	6.6±0.8
6 weeks	8.9±1.1	9.0±0.9	6.7±0.6
12 weeks	9.3±1.1	8.2±1.3	6.8±0.9
24 weeks	9.3±1.1	7.9±1.5	7.4±0.7

5

AMBIENT ROOM TEMPERATURE	Example 3	Example 4	Example 5
Initial	9.5±0.7	9.0±2.0	6.9±0.4
2 weeks	8.5±1.6	8.1±1.7	6.6±0.5
4 weeks	9.5±1.1	8.3 ±1.5	6.6±0.9
6 weeks	9.8±1.5	9.2±1.5	6.8±0.6
12 weeks	9.3±1.5	8.3±1.2	6.6±0.5
24 weeks	9.8±1.3	8.7±2.2	7.3±0.9

40°C OVEN	Example 3	Example 4	Example 5
Initial	9.5±0.7	9.0±2.0	6.9±0.4
2 weeks	9.7±1.2	9.3±1.8	6.9±0.7
4 weeks	9.9±1.0	9.6±1.3	7.2±0.9
6 weeks	10.1±1.2	9.6±1.7	7.4±0.5
12 weeks	9.6±1.3	9.7±1.9	7.2±1.2
24 weeks	10.2±1.7	9.2±1.7	7.7±0.9

10

WO 98/35666

PCT/US98/03388

Tablets of Examples 3-5 were tested for disintegration vs. time; results are shown hereunder.

DISINTEGRATION (kp)

REFRIGERATION	Example 3	Example 4	Example 5
Initial	3:13	0:48	1:00
2 weeks	3:26±0:50	1:01±0:13	2:04±0:24
4 weeks	5:03±0:30	1:04±0:05	1:53±0:33
6 weeks	3:19±0:30	1:06±0:17	1:53±0:32
12 weeks	3:37±0:46	1:00±0:06	1:42±0:15
24 weeks	3:05±0:28	2:07±0:31	2:11±0:15

5

AMBIENT ROOM TEMPERATURE	Example 3	Example 4	Example 5
Initial	3:13	0:48	1:00
2 weeks	4:39±0:23	1:00±0:13	1:56±0:32
4 weeks	2:56±0:34	1:01±0:05	1:56±0:19
6 weeks	3:27±0:18	1:01±0:04	1:53±0:16
12 weeks	3:38±0:30	0:56±0:07	2:02±0:11
24 weeks	3:15±0:28	1:16±0:25	1:41±0:10

40°C OVEN	Example 3	Example 4	Example 5
Initial	3:13	0:48	1:00
2 weeks	3:28±0:23	1:01±0:04	1:49±0:26
4 weeks	4:06±0:46	1:04±0:13	1:52±0:10
6 weeks	4:06±0:54	1:08±0:13	2:00±0:25
12 weeks	3:30±0:12	1:07±0:29	2:17±0:17
24 weeks	4:08±0:30	0:53±0:02	2:07±0:24

WO 98/35666

PCT/US98/03388

The tablets of Example 2 (RC/Naproxen NP) were comparatively tested against ALEVE® for hardness, disintegration and dissolution times. The results are shown in Table I.

TABLE I

TEST	TABLET
Hardness	
ALEVE®	14.4 Kp
RC/Naproxen NP	6.0 Kp
Disintegration Time	
ALEVE®	26 min.
RC/Naproxen NP	95 sec.
Dissolution*	
ALEVE®	80% in 11 min.
RC/Naproxen NP	80% in 7 min.

5 * Dissolution test was conducted in 0.1M phosphate buffer at pH 6.0.

Pharmacokinetic studies in beagles were conducted to define the absorption profile of Direct Compressed nanoparticulate naproxen caplets and to compare this profile to the profile obtained with the commercial product, ALEVE. The studies were conducted using art-accepted methods familiar to the pharmaceutical industry.

10

Plasma naproxen for each dog were modeled using the NONLIN84 method of Statistical Consultants, Inc. ("PCNONLIN and NONLIN84: Software for the Statistical Analysis of Nonlinear models, The American Statistician, vol. 40, No. 1 (1986)), using a one compartment model with first-order input, first-order output, and a lag period (Model 4, Figure 1). The following pharmacokinetic parameters were obtained; Volume (V), the absorption rate constant, K_{01} , the elimination rate constant, K_{10} and the apparent lag time, T_{lag} . There are five secondary parameters calculated; the are under the plasma curve, AUC, the half-life of absorption ($K_{10} t_{1/2}$), the half-life of elimination ($K_{10} t_{1/2}$), T_{MAX} and C_{MAX} . The dose (200,000 μ g) was the only constant.

15

20

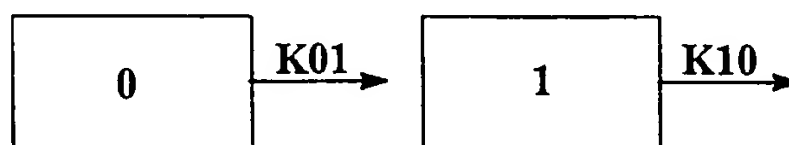
The absorption rate constant (K_{01}) and the absorption lag time, T_{lag} , obtained from the NONLIN model were then used to calculate the Mean Absorption Time; $MAT = 1/K_{01} + T_{lag}$. MAT will therefor inherently contain both the *in vivo* disintegration and dissolution time.

WO 98/35666

PCT/US98/03388

Figure 1

NONLIN84 Model 4: One-compartment with first-order input, first-order output



$$C(T) = D \cdot K_{01} / V / (K_{01} - K_{10}) \cdot (e^{-K_{10} \cdot T}) - (e^{-K_{01} \cdot T})$$

Where the estimated parameters are:

- (1) V = Volume
- (2) K_{01} = Absorption rate
- (3) K_{10} = Elimination rate
- (4) T_{lag} = Lag time

There is only one constant in input:

- (1) D = Dose

There are five secondary parameters:

- (1) $AUC = D / V / K_{10}$
- (2) K_{10} half-life
- (3) K_{01} half-life
- (4) T_{MAX} = time of maximum concentration
- (5) C_{MAX} = maximum concentration obtained

The data presented are the average values for T_{MAX} and C_{MAX} as estimated from NONLIN84, and the Mean Absorption Time (MAT), calculated from NONLIN84 estimates of K_{01} and T_{lag} . The data was obtained by comparing the tablets of Example 1 to ALEVE®, a commercial naproxen tablet, when administered to fasted and unfasted beagles.

WO 98/35666

PCT/US98/03388

**Oral Absorption Kinetics of ALEVE® and Tablets of Example 1
in the Fed and Fasted States in Dogs***

5

Parameter	ALEVE® Caplet		Tablets of Example 1	
	Fed (n=17)	Fasted (n=10)	Fed (n=5)	Fasted (n=5)
MAT ¹	31±30 (96.8% CV) ²	18±8 (44.4% CV) ²	14±2 (14.3% CV) ²	10±2 (20.0% CV) ²
T _{max}	122±99 (81.29% CV)	77±27 (35.1% CV)	53±16 (30.2% CV)	32±5 (15.6% CV)
C _{max}	79±8	82±8	77±7	69±7

* Dog absorption rate is approximately twice as fast as human absorption rate

1 Mean absorption time

2 CV = coefficient of variation

10

From the data, it is evident that the time to peak plasma concentration (T_{MAX}) was shorter for the present invention compared to the ALEVE® formulation of naproxen. The present invention also exhibits less variability in rate of absorption (MAT) and a reduced fed-
15 fasted difference.

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

20

WO 98/35666

PCT/US98/03388

WHAT IS CLAIMED IS:

1. A pharmaceutical tablet to decrease fed/fasted variability in absorption and decreased variability in absorption upon administration to a mammal comprising: naproxen particles
5 having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm; and a pharmaceutically acceptable carrier.
2. The pharmaceutical tablet of claim 1 having a pK parameter of time to peak plasma
10 concentration of less than about 2.0 hours.
3. The pharmaceutical tablet of claim 1 wherein the effective average particle size of said naproxen particles is less than 300 nm.
- 15 4. The pharmaceutical tablet of claim 1 wherein said surface modifier is present in an amount of 0.1 to 90% w/w based on the total weight of the dry particles.
5. The pharmaceutical tablet of claim 1 wherein said surface modifier is selected from polyvinylpyrrolidone and a block copolymer of ethylene oxide and propylene oxide.
20
6. The pharmaceutical tablet of claim 1 wherein said surface modifier is hydroxypropyl cellulose.
7. The pharmaceutical tablet of claim 1 formed by compression and comprising on a weight
25 per weight basis: 42 to 58 parts of nanoparticulate naproxen/surface modifier; from about 30-40 parts of filling agent; from about 10-15 parts of binding agent; 0.2 - 0.3 parts of lubricating agent; and 0-4 of other excipients.
8. The pharmaceutical tablet of claim 7 comprising: 200 mg of nanoparticulate naproxen; 15
30 mg of polyvinylpyrrolidone; 150 mg of lactose monohydrate; 50 mg of low-substituted hydroxypropyl cellulose; and 1 mg of magnesium stearate.
9. The pharmaceutical tablet of claim 1 formed by roller compaction and comprising on a
35 weight per weight basis: 65 to 80 parts of nanoparticulate naproxen/surface modifier; from about 10-20 parts of disintegrating agent; from about 5-20 parts of binding agent; 0.4 - 0.6 parts of lubricating agent; and 0-4 parts other excipients.

WO 98/35666

PCT/US98/03388

10. A method of treating a mammal comprising administering to the mammal an effective amount of the pharmaceutical tablet of claim 1.
11. A method of preparing the pharmaceutical tablet of claim 1 comprising the steps of:
- 5 (a) dispersing powdered naproxen in a liquid dispersion medium containing a surface modifier and wet grinding said naproxen in the presence of a rigid grinding media to an effective average particle size of less than about 400 nm, wherein the pH of said media is maintained within the range of from about 2 to 6 during said wet grinding;
- 10 (b) separating said surface modified naproxen particles from said grinding media;
- (c) spray drying the surface modified naproxen particles;
- 15 (d) screening the surface modified naproxen particles to obtain uniform particles of less than about 20 mesh;
- (e) blending said particles with tableting excipients; and
- 20 (f) compressing the uniform particles into tablets.
12. The method of claim 11 further comprising film coating the tablets with a biodegradable film forming material.
- 25 13. The method of claim 11 wherein said spray drying comprises the steps of:
- (a) feeding nanoparticulate suspension and a stabilizer into an atomizer to produce a fine spray of droplets;
- 30 (b) evaporating moisture from said droplets; and
- (c) drying the nanoparticulates to obtain nanoparticles suspended in a solid polymer matrix of the stabilizer.
- 35 14. The method of claim 11 wherein said stabilizer is polyvinylpyrrolidone.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/03388

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/19 A61K9/14 A61K9/51 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 24336 A (NANOSYSTEMS LLC) 15 August 1996 * see in particular example 1 *	1-4, 6, 10, 11
X	WO 96 24339 A (NANOSYSTEMS LLC) 15 August 1996 * see in particular preparation 1, example 2 *	1-5
X	WO 93 25190 A (STERLING WINTHROP INC) 23 December 1993 *see in particular example 1; p. 11, 1.22-35 *	1-5
X	US 5 510 118 A (BOSCH H WILLIAM ET AL) 23 April 1996 *see in particular col. 7, l. 38 - col. 9, l. 40 *	1-6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

14 April 1998

Date of mailing of the international search report

30. 04. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, T.x. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Isert, B

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/03388

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9624336 A	15-08-1996	US 5591456 A AU 4866796 A	07-01-1997 27-08-1996
WO 9624339 A	15-08-1996	US 5518738 A AU 4900996 A CA 2212779 A EP 0808156 A	21-05-1996 27-08-1996 15-08-1996 26-11-1997
WO 9325190 A	23-12-1993	AT 150297 T AU 677783 B AU 4396493 A CA 2118517 A DE 69309056 D DE 69309056 T EP 0644755 A ES 2101323 T HU 70952 A JP 8501073 T MX 9303452 A US 5552160 A	15-04-1997 08-05-1997 04-01-1994 23-12-1993 24-04-1997 18-09-1997 29-03-1995 01-07-1997 28-11-1995 06-02-1996 31-01-1994 03-09-1996
US 5510118 A	23-04-1996	AU 4867396 A WO 9625152 A	04-09-1996 22-08-1996